miRNAs regulate SIRT1 expression during mouse embryonic stem cell differentiation and in adult mouse tissues.

Journal: Aging (Albany NY)

Publication Year: 2010

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PubMed link: 20634564

Funding Grants: Molecular dissection of adult liver regeneration to guide the generation of hepatocytes from pluripotent stem cells, Gladstone CIRM Scholar Program

Public Summary:
The study shows that SIRT1 is expressed in mouse embryonic stem cells but suppressed by microRNAs in differentiated cells. Accordingly, reprogramming of fibroblasts to pluripotency induces SIRT1 expression. The findings suggest microRNAs as targets for modulation of SIRT1 expression and potentially also for reprogramming.

Scientific Abstract:
SIRT1 is increasingly recognized as a critical regulator of stress responses, replicative senescence, inflammation, metabolism, and aging. SIRT1 expression is regulated transcriptionally and post-transcriptionally, and its enzymatic activity is controlled by NAD+ levels and interacting proteins. We found that SIRT1 protein levels were much higher in mouse embryonic stem cells (mESCs) than in differentiated tissues. miRNAs post-transcriptionally downregulated SIRT1 during mESC differentiation and maintained low levels of SIRT1 expression in differentiated tissues. Specifically, miR-181a and b, miR-9, miR-204, miR-199b, and miR-135a suppressed SIRT1 protein expression. Inhibition of mir-9, the SIRT1-targeting miRNA induced earliest during mESC differentiation, prevented SIRT1 downregulation. Conversely, SIRT1 protein levels were upregulated post-transcriptionally during the reprogramming of mouse embryonic fibroblasts (MEFs) into induced pluripotent stem (iPS) cells. The regulation of SIRT1 protein levels by miRNAs might provide new opportunities for therapeutic tissue-specific modulation of SIRT1 expression and for reprogramming of somatic cells into iPS cells.